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Treating attention-deficit/hyperactivity disorder beyond symptom control alone in children and adolescents: a review of the potential benefits of long-acting stimulants

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Abstract Attention-deficit/hyperactivity disorder (ADHD), one of the most common neuropsychiatric conditions of childhood, often has a chronic course and persists into adulthood in many individuals. ADHD may have a clinically important impact on health-related quality of life in children, a significant impact on parents' emotional health and interfere with family activities/cohesion. To date, the main targets of ADHD treatment have focused on reducing the severity of symptoms during the school day and improving academic performance. However, the treatment of ADHD should reach beyond symptom control to address the issues of social competencies and improvement of health-related quality of life from the perspectives of individuals with ADHD and their families, to support them in reaching their full developmental potential. Methylphenidate (MPH) is recognised as the first-line choice of pharmacotherapy for ADHD in children and adolescents. This paper focuses on the importance and benefits to child development of ADHD symptom control beyond the school day only, i.e. extending into late afternoon and evening and uses the example of an extended-release MPH formulation (OROS[®] MPH) to demonstrate the potential

benefits of active full day coverage (12 h) with a single daily dose. Concerns of long-term stimulant treatment are also discussed.

Keywords ADHD · Children · Quality of life · Methylphenidate · OROS[®] MPH

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric conditions of childhood, with prevalence generally estimated at 4–12% [8, 13, 28, 58, 81]. ADHD is characterised by a chronic pattern of symptoms of inattention, impulsivity and hyperactivity, which are more present than absent in affected individuals [2]. The differentiation between ADHD and normal behaviour is based on the frequency of inappropriate behaviour, according to norms for age and IQ, and on the resulting impairment of functioning in different settings, for example, the child's behaviour and ability to accomplish tasks at home, at school, or in the community. Children with ADHD frequently have a number of co-existing disorders, such as conduct disorder, anxiety, depression, oppositional defiant disorder and obsessive disorder [12]. ADHD has also been associated with substance abuse and criminal behaviour [37, 59, 69]. Moreover, compared with non-affected children and adolescents, those with ADHD are at higher risk of sustaining accidental injuries, and requiring emergency department visits and hospitalisations [20, 41].

The effects of ADHD on a child's development may be far-reaching. While some effects are a direct consequence of the condition itself (e.g. poor classroom behaviour, impaired executive functioning and decreased classroom

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productivity), many relate to the resulting impairment of social interactions, academic achievement and emotional development [6]. Data suggest that children with ADHD are more likely to function poorly at home and at school, disrupt family and peers relationships, and suffer from low self-esteem [37, 45, 62]. Indeed, such findings were highlighted by the results of a recent pan-European survey, in which parents of children (8–18 years) with ADHD and without ADHD (normative population sample) completed an on-line questionnaire about the impact of their child's ADHD on everyday activities, general behaviour and family relationships [19]. Compared with the normative population sample, parents reported that ADHD children consistently displayed more demanding, noisy, disruptive, disorganised and impulsive behaviour. Likewise, a number of everyday activities (meal times, homework, playing alone, playing with other children, following family routines, individual leisure activities and group leisure activities) were also reported to be adversely affected by ADHD. Furthermore, parents reported that ADHD impacted negatively on all relationships, particularly those between the parent and child, child and their siblings and the child and other children [19].

From an early age, children with ADHD exhibit difficulties with attention and impulse control, and in modulating their behaviour as the situation demands. Evidence suggests that unless children achieve minimal social competence by around the age of 6–8 years, they have a high probability of being at risk of social difficulties throughout life [36]. While the child–parent relationship is important for personality development, peer relationships make a large contribution to social and cognitive development, being an integral part of good social competencies. Indeed, the single best childhood predictor of adult adaptation may not be IQ, academic success, or classroom behaviour, but the adequacy with which a child interacts with other children [36]. As such, children who are aggressive and disruptive, unable to sustain close relationships with other children and who cannot establish a place for themselves in peer culture are seriously 'at risk'.

This paper focuses on the importance and benefits to child development of managing ADHD symptoms beyond the school day only, i.e. extending into late afternoon and evening. Given the potential advantages of managing ADHD symptoms outside of the school environment, there has recently been great interest in the use of long-acting stimulant preparations. Indeed, current international guidelines for the management of ADHD recommend the use of long-acting formulations to reduce the need for in-school dosage and the likelihood of diversion [53, 70]. To date, a number of long-acting methylphenidate (MPH) formulations, with different pharmacological profiles, have been developed, including Equasym XL[®], Ritalin LA[®],

Metadate CD[®] and Concerta XL[®]. This paper discusses the benefits of the use of long-acting MPH preparations, especially OROS[®] MPH, to exemplify the potential advantages of coverage over the active day for the child or adolescent with ADHD.

Extending the period of symptom control

The treatment of children with ADHD requires a comprehensive multimodal approach in which pharmacotherapy is an integral part of the treatment plan [70, 79, 104]. Current treatment guidelines suggest that children with ADHD benefit from medical therapy with MPH [33, 90]. Atomoxetine, a non-stimulant norepinephrine-specific re-uptake inhibitor, is also approved for the treatment of ADHD in children aged ≥ 6 years and adolescents [16].

Pharmacotherapy for attention-deficit/hyperactivity disorder

Effects of atomoxetine and methylphenidate on attention-deficit/hyperactivity disorder

Newcorn et al. [72] performed a large placebo-controlled, double-blind, cross-over study to compare the response rates of OROS MPH and atomoxetine, in patients with ADHD (aged 6–16 years). After 6 weeks of treatment, the proportion of patients responding to OROS MPH was significantly higher than the proportion of patients responding to atomoxetine (56 vs. 45% respectively; $P = 0.02$). For patients previously treated with a stimulant ($n = 301$), the response rate compared to placebo was significantly greater for OROS MPH (51 vs. 23%, respectively; $P = 0.002$) but not for atomoxetine (37 vs. 23%, respectively; $P = 0.09$). The response rate for OROS MPH was higher to that for atomoxetine ($P = 0.03$). In patients who were stimulant-naïve at study entry ($n = 191$), the response rates for both atomoxetine (57%; $P = 0.004$) and OROS MPH (64%; $P \leq 0.001$) were superior to the rate for placebo (25%). The response rates for OROS MPH and atomoxetine were not significantly different ($P = 0.43$). There were no significant group differences in completion rates (atomoxetine 84%, OROS MPH 82%, placebo 77%; $P = 0.42$). In addition, the rates of discontinuation due to adverse events were low and similar for all treatments (atomoxetine 2%, OROS MPH 2%, placebo 3%; $P = 1.00$). In the second phase of the study, patients who were initially randomized to OROS MPH and completed the 6-week study were switched to atomoxetine ($n = 178$). At the end of the second phase, 34% of the patients switched to atomoxetine responded to either atomoxetine or

OROS MPH but not both, 44% responded to both treatments and 22% did not respond to either treatment. Of the 70 patients who did not respond to OROS MPH in the initial trial, 43% subsequently responded to atomoxetine. Likewise, 29 (42%) of the 69 patients who did not respond to atomoxetine had previously responded to OROS MPH. Atomoxetine and OROS MPH both produced robust improvements in symptoms in patients with ADHD; however, there was a statistically significant difference in efficacy (response) favouring OROS MPH. Data from the second part of the study suggest that there is a differential response to the two treatments in approximately one-third of patients [72]. This finding is consistent with practice guidelines that recommend changing to a different class of medication if there is poor response to or tolerance of the first agent used.

Kemner et al. [48] performed a large, community-based, open-label study to evaluate treatment outcomes in children (aged 6–12 years) with ADHD, randomized to either once-daily OROS MPH ($n = 850$) or atomoxetine ($n = 473$) for 3 weeks. To simulate clinical practice, investigators were allowed to select starting doses on the basis of their clinical judgment within the approved dose ranges of each drug. Investigator-rated ADHD rating scale (ADHD-RS) assessments showed that, compared with baseline scores, both treatments produced statistically significant reductions in ADHD symptoms at each time point. However, the OROS MPH group resulted in significantly greater reductions from baseline in ADHD-RS scores throughout the course of the study compared to the atomoxetine group [48]. At the primary endpoint (week 3), mean changes from baseline in ADHD-RS scores were 20.24 points for OROS MPH and 16 points for atomoxetine ($P < 0.001$). Statistically significant differences between treatment groups were also observed at week 1 and 2 ($P < 0.001$), and a posthoc analysis indicated that between-treatment differences increased over time (2.77, 3.44 and 4.24 at weeks 1, 2 and 3, respectively; $P < 0.001$). Subgroup analyses, based on previous treatment for ADHD, demonstrated that, in subjects with a history of stimulant usage, reductions in ADHD-RS scores were significantly greater for OROS MPH versus atomoxetine at weeks 1, 2 and 3, whereas in subjects who were previously treatment-naïve reductions in ADHD-RS scores were significantly greater for OROS MPH versus atomoxetine at week 3 only. It should be pointed out that, as the authors themselves state, the duration of the study may not have been sufficient, and the 3-week timepoint may, therefore, not have been representative of the full action of atomoxetine. The incidence of treatment-related adverse events did not differ significantly between groups (OROS MPH 22.5%; atomoxetine 25.6%). Most adverse events were categorised

as mild and not serious [48]. In line with the findings of Newcorn et al., these results suggest greater ADHD symptom improvement with OROS MPH than with atomoxetine.

Wang et al. [112] conducted a 10-month randomised, double-blind study in outpatients with ADHD (aged 6–16 years) in China, Korea and Mexico to (1) examine whether atomoxetine is non-inferior to MPH in treating symptoms of ADHD, and (2) determine the tolerability of the two drugs. Patients were randomly assigned to once-daily atomoxetine (0.8–1.8 mg/kg per day; $n = 164$) or twice-daily MPH (0.2–0.6 mg/kg per day; $n = 166$). Primary efficacy assessment was the comparison of response rates ($\geq 40\%$ reduction from baseline to endpoint in total score) on the parent-rated ADHD-RS. Results demonstrated that atomoxetine was non-inferior to MPH in improving ADHD symptoms based on response rates (atomoxetine 77.4%; MPH 81.5%; $P = 0.404$). Treatment-emergent adverse events experienced significantly more frequently in the atomoxetine group compared with the MPH group, included anorexia (37.2 vs. 25.3%; $P = 0.024$), nausea (20.1 vs. 10.2%; $P = 0.014$), somnolence (26.2 vs. 3.6%; $P < 0.001$), dizziness (15.2 vs. 7.2%; $P = 0.024$) and vomiting (11.6 vs. 3.6%; $P = 0.007$). Atomoxetine-treated patients also experienced a small but significantly greater mean weight loss from baseline to endpoint than MPH-treated patients (−1.2 vs. −0.4 kg; $P < 0.001$) [112].

Two further open-label studies have also examined the efficacy and safety of atomoxetine and MPH in children with ADHD [52, 93]. Results from the first study by Kratochivl et al., which was a 10-week, prospective, randomised, open-label trial in 228 children with ADHD, reported that both atomoxetine ($n = 184$) and MPH ($n = 44$) were associated with marked improvement in inattentive and hyperactive-impulsive symptom clusters as assessed by parents and investigators. However, no statistically significant differences between treatment groups were observed on the primary outcome measure (investigator rated ADHD-IV rating scale total score). Safety and tolerability were also similar between the two agents [52]. The second study, a subgroup analysis of the Kemner [93] study, was a 3-week, multicentre, randomised, open-label study that assessed treatment outcomes with OROS MPH ($n = 125$) and atomoxetine ($n = 58$) in African-American children with ADHD. Both treatments were associated with significant improvements in ADHD symptoms from baseline. However, patients who received OROS MPH demonstrated significantly greater improvements in total ADHD symptoms, inattentiveness and global improvement. The incidence of adverse events was similar in both treatment groups [93].

Focus on methylphenidate for attention-deficit/hyperactivity disorder

MPH is the most frequently prescribed psychostimulant, and there is a substantial evidence base for the efficacy of MPH over treatment periods of up to 1 year and at doses of up to 60 mg/day [103]. Both short- and long-acting (LA)/extended-release (ER) formulations are available. Behavioural improvements resulting from treatment with psychostimulants include sustained attention, impulse and emotional control, reduction of task-irrelevant activity, diminishment of noisy and disruptive behaviour, and diminishment of aggression [5, 74]. Other benefits include improvements in working memory, persistence of effort, academic productivity, accuracy and handwriting [5, 38]. As a result of stimulant treatment, children with ADHD may become more compliant with parental and teacher instructions, be better able to sustain such compliance, and often become more cooperative with others [5]. Furthermore, ADHD children themselves describe improvements in their self-esteem as a result of symptom control with stimulant medication [5]. Consequently, the quality of social interactions, such as peer relations, is improved [5, 103]. Common side effects of psychostimulants include appetite loss, stomach ache, insomnia and headache [5]. Rebound hyperactivity and irritability may also occur as the medication wears off, and pre-existing tic disorders can be exacerbated in certain children [119].

In the multimodal treatment study of children with ADHD (MTA) [104], community care group subjects, who were treated by their own providers, principally received treatment with immediate-release (IR) MPH, which was administered at an average of 2.3 doses per day (i.e. providing approximately 8-h coverage). The medical management group received IR MPH three-times daily, which provides 10–12-h coverage. Since medical management fared substantially better than community care on most ADHD outcome measures at 14 months of treatment, it might be inferred that improved symptom control is provided by extended treatment coverage, although the study was not designed to test this hypothesis. In addition, it should be noted that a prospective follow-up study, which was undertaken to determine any long-term effects, 6 and 8 years after childhood enrolment, of the randomly assigned 14-month treatments in the MTA study demonstrated that the originally randomized treatment groups did not differ significantly on repeated measures or newly analysed variables such as school grades, arrests, psychiatric hospitalisations and other clinically relevant outcomes [64].

In general, the effects of MPH usually last only about 4 h with an IR formulation, although 12-h coverage may be provided with three-times daily dosing [120]. However, a

two- or three-times daily dosing regimen results in peaks and troughs in plasma concentrations, which might lead to ‘waxing and waning’ of behavioural symptom improvement throughout the day and, potentially, to rebound [98]. Optimal IR dosing may, therefore, require taking the next dose before the previous dose begins to wear off. The development of LA/ER preparations has allowed continuous effective management of the symptoms of ADHD over a longer time period, although their duration of effect varies [4]. In general, Metadate CD (Equasym XL) and Ritalin LA provide 8-h coverage, although their effect can be extended by the addition of an IR dose. OROS MPH provides 12-h coverage with a single daily dose [120]. OROS MPH delivers MPH in a unique pattern of immediate-release (a small bolus) followed by extended-release (ascending delivery profile). Delivery of an ascending drug delivery profile has been claimed to provide optimal efficacy over 12 h, for example, from early morning through the period of homework and after-school social activities [77, 97].

Psychosocial treatments for ADHD

Although stimulant medication is the cornerstone of treatment for ADHD, numerous nonpharmacological treatments can be employed in combination with medication to assist in the lifelong management of the disorder. Today, a large evidence base exists for behavioural interventions, including parent training in effective child behaviour management, family therapy in problem solving and communication skills and school interventions, such as classroom behaviour medication methods and academic interventions, which has resulted in their classification as ‘empirically validated treatments’ [7, 18, 66]. In addition, social skills training with generalisation components, intensive summer treatment programmes and educational interventions have also shown promise in the treatment of ADHD [18].

Targets of therapy and the potential advantages of extending the period of symptom control

Social competence

As children should achieve minimal social competence by the age of 6–8 years to avoid being ‘at risk’ of social difficulties throughout life [36], an important outcome of a comprehensive ADHD treatment programme is the all-round personality development of affected children and adolescents. Social and family functioning should, therefore, be included alongside school performance as goals of ADHD treatment. The time after school, when life may be

less structured, is just as important as school time for a child with ADHD, in terms of developing personal and social skills. Treatment that lasts the full day might enable patients to develop both academic and social skills, thereby improving both functioning in and out of school and child–peer and child–parent interactions. Indeed, sustained improvements (up to 12 months) in global assessment scale scores and peer interaction have been reported in children with ADHD receiving OROS MPH [115]. Such an ADHD treatment option has been shown to improve driving performance and reduce the risk of car accidents [20, 37, 59, 67, 71].

Although appropriate treatment would also be expected to minimise the potential risk for drug and alcohol abuse and criminality [10, 116], this was not found to be the case in a recent study that compared delinquent behaviour and early substance use between children in the MTA study ($n = 487$; total population, i.e. including those who received medication and/or behavioural treatment, or standard community care) and those in a local normative comparison group ($n = 272$). Relative to the local normative comparison group, children in the MTA study demonstrated significantly higher rates of delinquency (27.1 vs. 7.4% at 36 months; $P = 0.000$) and substance abuse (17.4 vs. 7.8% at 26 months; $P = 0.001$), suggesting that the cause-and-effect relationships between treatment for ADHD and delinquency are unclear [63].

Reduction of specific behaviours and/or symptoms of attention-deficit/hyperactivity disorder throughout a 12-h day

Two laboratory school studies have demonstrated that attention and behaviour improved significantly and were sustained for 12 h, covering the school day, homework and other after-school activities, when children took OROS MPH once daily compared to placebo [77, 97].

In addition, once-daily treatment with OROS MPH has been shown to be at least as effective as IR MPH given three-times a day in double-blind studies. Results from a double-blind, within-subject study of the efficacy and duration of action of IR MPH three times a day and once-daily OROS MPH, compared with placebo, demonstrated that on virtually all measures in natural and structured (laboratory) settings, both drugs were significantly different from placebo, but not different from each other [77]. These results were confirmed in a 28-day, double-blind clinical trial in 282 children, randomised to placebo, IR MPH three times a day, or OROS MPH once daily [121]. More recently, a prospective cross-over study of 30 children also demonstrated that ER MPH formulations (Ritalin LA, OROS MPH) provided an improvement for patients, which is in keeping with Ritalin IR efficacy

through once-daily administration [29]. However, a 1-month switching study (from IR MPH to OROS MPH) indicated that, unlike IR MPH, OROS MPH improved symptom control in the after-school period [84]. However, it is important to note that this was an open-label, non-randomized, dose-adjustment study and the extent to which raters may have been biased by their knowledge of medication cannot be assessed [84]. Similarly, results from a prospective study demonstrated that OROS MPH was effective during the late afternoon and homework time, and consistent with parents' preference, was finally prescribed in over twice as many children as Ritalin LA [29]. This management strategy has been substantiated in a randomized, controlled effectiveness trial of OROS MPH compared to usual care with IR MPH in children with ADHD [94]. Overall, OROS MPH showed statistically significant superiority to IR MPH on multiple outcome measures, including remission rate. Recent evidence from a 28-day, open-label trial suggests that behavioural improvements observed when children with ADHD are switched from IR MPH to OROS MPH may also be accompanied by improvements in neurocognitive function, although these findings have yet to be replicated in large-scale, controlled trials [49].

Of note, an open-label study that evaluated the tolerability and effectiveness of once-daily OROS MPH in children with ADHD reported that effectiveness was maintained throughout 12 months, as demonstrated by stable inattention and overactivity with aggression scale (IOWA), Conners ratings and sustained improvements in peer interaction and global assessment scale scores [115]; analysis at 24 months also demonstrated effective symptom control [114]. A large, double-blind, placebo-controlled, multicentre trial also confirmed the efficacy and safety of OROS MPH in the treatment of adolescents with ADHD [118].

Comorbid anxiety

Attention-deficit/hyperactivity disorder is associated with a high risk of psychiatric comorbidity, which extends past childhood and adolescence into adulthood [9]. Reports of the impact of comorbid anxiety on MPH treatment of ADHD (and vice versa) have been variable. A randomized, double-blind, placebo-controlled, crossover study, conducted in 22 nonanxious and 18 anxious children with ADHD, found that comorbid anxiety was associated with a less robust response to MPH treatment, particularly in terms of improvement of working memory [102]. Similarly, a short-term, fixed-dose investigation, conducted in 43 children with ADHD, found that subjects with comorbid anxiety had a significantly poorer response to MPH than those without anxiety [80]. Furthermore, a study comparing 20 children with ongoing core symptoms of ADHD, who

had received ≥ 6 months of psychostimulant treatment, with 20 age- and IQ-matched medication-naïve controls found that anxiety was significantly increased in children with ADHD who were treated with psychostimulant medication in the intermediate to long term [109]. Other studies have found that response to MPH in children with ADHD is unaffected by the presence of comorbid anxiety. For example, the MTA study found that stimulant medication was equally effective in reducing ADHD symptoms in patients with and without comorbid anxiety [44, 104]. Similarly, a 4-month, randomized, placebo-controlled trial, conducted in 91 children with ADHD, 38 of whom had comorbid anxiety, found that, when MPH dose is titrated as in standard clinical practice, the presence of comorbid anxiety influenced neither the efficacy nor the associated side effects of MPH treatment [23]. Furthermore, a study investigating the efficacy of sequential pharmacotherapy in 42 children with ADHD and comorbid anxiety not only found that response to MPH treatment was comparable with that observed in children with general ADHD, but also that a small but significant minority of children exhibited a clinically meaningful reduction in anxiety following treatment with stimulant monotherapy [1]. Suggested reasons for these discrepancies include differences in study design (e.g. the MTA study included individualised titration, 14 months of treatment and a monthly management strategy), in contrast to the short-term, fixed-dose designs of earlier investigations [104] and the fact that children with ADHD and comorbid anxiety are likely to present with more physiological symptoms than those without comorbid anxiety, which may be overlooked at the time of treatment initiation and subsequently incorrectly attributed to the treatment itself [23]. Further investigations, particularly over the longer term, are required in order to further clarify the interaction between MPH treatment and comorbid anxiety.

Promotion of overall well-being, health and resilience of children and adolescents

The measurement of ADHD treatment response is often limited to measuring symptoms; therefore, because so much focus has been on symptom reduction, less is understood about health-related quality of life (HRQoL) and functioning. In a survey of 131 children with ADHD, 68.7% of whom had a comorbid psychiatric disorder, the parent version of the child health questionnaire was used to measure physical health, psychosocial health, limitations in family activities and family cohesion [50]. Compared with children without ADHD, children with ADHD had comparable physical health, but clinically important deficits in HRQoL in all psychosocial domains, including role/social limitations as a result of emotional behavioural problems

(self-esteem, mental health and general behaviour). In addition, children with ADHD had a significant impact on parents' emotional health and time to meet their own needs, and interfered with family activities and cohesion. Of note, results from a recent meta-analysis, which was undertaken to determine the relationship between a reduction of ADHD symptoms (assessed by the ADHD rating scale-IV-parent version [ADHDRS-IV-Parent:Inv]) and improvements in functioning [assessed by the life participation scale for ADHD (LPS)] reported that patients' symptomatic improvements were reflected in improvements in their social and behavioural function as measured by the LPS. Correlation analysis revealed a moderate-to-strong association between changes in the LPS total versus ADHDRS-IV-Parent:Inv total ($r = -6.8$) [14]. For a clear improvement in functional outcomes to become apparent, a decrease in ADHDRS-IV-Parent:Inv total of 16–18 points was necessary, corresponding to a symptomatic score reduction of approximately 40–45% [14].

A treatment offering effective symptom control throughout a 12-h day has the potential to promote feelings of well-being, good health and resilience and improved functioning among individuals with ADHD, although this association will need to be investigated further in future clinical trials. In a population that is already vulnerable to low self-esteem and problematic peer relationships [37, 45, 62], children with ADHD are likely to feel embarrassed by having to present themselves to a member of school staff every lunch-time to receive their medication [87]. The social stigma of having a psychiatric disorder can be particularly problematic for children and adolescents when they are at school or college and can lead to teasing and bullying by peers [97]. Moreover, aggressive and disruptive individuals with ADHD may not be accepted by their peer groups at school/college and after school/college activities and are, therefore, less likely to form close relationships. Indeed, in a study of 111 children with ADHD and 100 adolescents without an ADHD history [3], parents of probands reported fewer close friendships and greater peer rejection compared with the non-ADHD group, while probands reported that their friends were less involved in conventional activities compared with the non-ADHD group.

Compared to age-matched individuals without ADHD, young drivers with ADHD are 2–4 times more likely to have experienced a motor vehicle accident, over three-times more likely to have incurred associated injuries and four-times more likely to have been at fault for such accidents [67, 68]. In a randomized, crossover, single-blind pilot study, six male adolescents treated with OROS MPH demonstrated significantly less variability in driving performance and performed significantly better throughout the day (e.g. steering, braking, speed and collisions) than

patients treated with IR MPH three-times daily, particularly in the evenings (at 20:00 h) [22]. In another study, the effects of OROS MPH, stimulant mixed amphetamine salts extended release (MAS XR) or placebo on driving were compared in 35 adolescents with ADHD using a driving simulator at 17:00, 20:00 and 23:00 h. OROS MPH resulted in less time driving off the road, fewer instances of speeding, less erratic speed control and less inappropriate use of brakes when compared with placebo. In terms of overall driving performance, OROS MPH was significantly superior to placebo, whereas MAS XR was not associated with better driving than placebo [21]. These findings were considered to be due to the once-daily delivery of OROS MPH, which was designed to provide 12 h of continuous symptom control. OROS[®] MPH has also been shown to significantly improve driving performance compared with placebo and MAS XR [21].

Whilst debilitating for the child, ADHD has also been shown to adversely impact on parents' quality of life, placing a substantial burden on the family as a whole. Compared to parents with children with no significant problem behaviours, parents with children with externalising behaviours (e.g. hyperactivity, aggression) reported a more negative impact on social life, more negative and less positive feelings about parenting and higher child-related stress [24]. Moreover, some parents of ADHD children have reported levels of stress as high as those reported by parents of children with autism [24].

Compounding these effects, the behaviour of parents and teachers towards children with ADHD is likely to be different from that with those without ADHD; such reactions may exacerbate the reduction in overall functioning and quality of life of those involved. In a study examining the behaviour of children with externalising disorders in interaction with their mothers, hyperactivity was enhanced by the interaction between the impulsive behaviour of the child and the aversive maternal response [106]. Mothers of children with ADHD were more restrictive and negative towards their children and showed less adequate control than did mothers of children without externalising disorders. ADHD children paid less attention, were less assertive and helpless and were more impulsive than controls. The importance of changes in parenting behaviour for families of children with ADHD has been highlighted during the MTA study which examined treatment outcomes for objectively measured parenting behaviour [113]. The combination of medication management and intensive behaviour therapy produced significantly greater improvements in constructive parenting than did either treatment alone.

Symptom management that extends beyond the school day will enable children and adolescents to focus on their homework and achieve better academic grades. Such

improvements in performance may result in feelings of self-satisfaction and increase self-confidence. Moreover, social acceptance, good relationships with peers and with families, and academic achievements may further reduce anxieties linked to poor relationships and underperformance.

Adherence

The requirement for multiple daily dosing of MPH increases the likelihood of poor adherence, particularly in adolescents, and poor persistence with therapy has been shown to be associated with increased maternal psychological distress, indifferent parenting, maternal overprotection/control, poor family support, decreased interaction with parents and increased problems at home [32]. In order to improve compliance, once-daily administration of MPH is required [32]. Indeed, compliance has been shown to be significantly better for patients with ADHD receiving OROS MPH than IR MPH [54], and the switching of children with poor adherence to IR MPH to OROS MPH is associated with a significant improvement in behavioural symptoms and family/school measures [17]. In addition, initial treatment with an ER MPH has been associated with longer treatment periods, fewer switches in therapy, increased patient persistence with therapy and a lower usage rate of emergency room services compared with initial treatment with IR MPH [47].

Patient preference

Clearly, taking a medication once a day is more convenient for both the individual taking the medication and for those having to administer it [97]. For the school, the inconvenience and responsibility of storing and dispensing a controlled medication is removed [56]. Indeed, in a 9-month open-label study involving over 1,000 individuals treated with OROS MPH, more than 86% of parents at 3 months gave increased convenience as a major reason for their preference [97]. Another study ($n = 1,082$) demonstrated that 77% of parents preferred OROS MPH to previous treatments, with convenience (86%), duration (75%) and smoothness (71%) of effect being the main reasons for their choice [85]. Furthermore, preference rates of parents (of 64 children) for OROS MPH over IR MPH taken three-times daily have been shown to be significant in a double-blind, cross-over study (54 vs. 26%, respectively; $P < 0.05$).

Embarrassment and stigma

MPH formulations requiring two- or three-times daily administration schedules require individuals with ADHD to

take their medication at school or college. However, children and adolescents may not want to take their medication because it makes them feel different from their peers. In addition, the stigma of being an outsider, or being different from their peers, increases non-adherence with medication. A survey of attitudes of children to taking stimulant medication revealed that the majority disliked taking medication; 59% of parents believed that their child's self-esteem suffered, while 68% of parents felt that their child was embarrassed by taking their medication [87]. The 12-h coverage provided by OROS MPH should be enough to make additional doses at school or college unnecessary, enabling treatment to be taken in the privacy of the home environment. This avoids the embarrassment of having to take medication in public and the associated stigma attached to having a psychiatric condition requiring medication [97].

Development of social and personal skills

Importantly, a therapy for ADHD should provide symptom control over the active day extending into the late afternoon and evening, i.e. time after school, when life is less structured. Indeed, results from the pan-European survey reported that 35–40% of parents stated that their child's ADHD symptoms needed to be more effectively treated during the afternoon and evening [19].

Such time is just as important as school time for a child in terms of building social and personal skills, including relationships with peers and family [36]. It may also allow for continued academic achievement, as it is designed to enable the child to better focus during homework time.

Extended symptom control in children and adolescents were reported in a study that assessed the impact of switching from IR MPH (10–60 mg/day) to OROS MPH (18, 36 or 54 mg once-daily) [84]. Decreases in the two subsets (inattention/overactivity and oppositional/defiance) of the parent/caregiver IOWA Conners ratings were reported, while IOWA Conners teacher ratings were maintained. Consistent with the 12-h duration of action [77, 97, 120], changes in the parent/caregiver IOWA Conners ratings suggest that OROS MPH improves symptom control in the after-school period. This has also been demonstrated in a 3-week open-label study in which children and adolescents were switched from IR MPH to OROS MPH [39]. Switching medication resulted in a significant positive effect as evidenced by caregivers' ratings of core symptoms on the IOWA Conners inattention/overactivity subscale. Corresponding ratings by teachers revealed the efficacy of OROS MPH was comparable to that of IR MPH. Global efficacy was rated as good/excellent by teachers

for 55% of the cases, by caregivers for 79% and by investigators for 77%. Given that previously the efficacy of OROS MPH has been shown to be comparable to IR MPH dosed three-times daily in children [77, 97, 121], lower ratings by teachers than parents/caregivers might have reflected differences in children's behaviour in the different environments.

Acute tolerance

There is suggestion that acute tolerance to MPH can develop over the course of the day, and that the method of MPH delivery determines whether efficacy is maintained during the afternoon [98]. Increasing the concentration of MPH throughout the day is thought to overcome the development of acute tolerance [99]. This has been demonstrated with the OROS preparation of MPH, which provides an initial low-dose MPH bolus and an ascending MPH delivery profile across the day, and maintains full efficacy for 12 h with once-daily oral administration [99].

Other considerations

In the same way that measurement of response to treatment has focused on symptoms rather than overall HRQoL, emphasis has also been given to measuring academic improvement as opposed to psychosocial impairment. In parallel, once-daily ER MPH formulations, with an effective duration of action of about 8 h, have been developed. Consequently, these formulations have been positioned mainly to improve school performance, an area of obvious concern in individuals with ADHD. As MPH is a stimulant and a controlled substance, with possible adverse consequences, such formulations also aim to provide low drug exposure, in line with potential concerns over the safety and long-term effects of treatment.

Developments, such as OROS MPH, enable clinicians to extend symptom control beyond the school day into the late afternoon and evening [77, 99]. This may result in additional beneficial effects on an individual's physical, emotional and social well-being later in the day (Table 1), an increasing area of interest that remains to be examined in future clinical trials.

Child health measures, such as the child health questionnaire [55] and the child health and illness profile [92], have been developed to evaluate HRQoL from childhood through adolescence. By assessing the individual's physical, emotional and social well-being from the perspective of a parent, or the child/adolescent directly, such questionnaires are helpful in evaluating treatment interventions. The current move towards their incorporation in to clinical trials has been long awaited.

Table 1 Potential benefits of symptom control extending into the evening for children and adolescents with attention-deficit/hyperactivity disorder

- Improved health (e.g. fewer comorbidities)
- Improved physical well-being, enabling greater participation in sporting activities
- Greater ability to focus later in the day on learning activities (e.g. homework), skilled activities (e.g. driving) and domestic activities
- Improved self-esteem, which may promote the desire for greater social interaction
- Enhanced feelings of well-being and a positive state of mind, which might encourage social interaction and improve relationships
- Increased ability and desire to meet friends later in the day
- Reduction in the risk of antisocial behaviour and involvement with the police
- Greater inclusion in everyday interactions with family members, improving the cohesiveness of the family unit

Concerns of long-term stimulant treatment

Medical concerns of full-day coverage with methylphenidate

Insomnia

Sleep disturbances are frequently reported by children with ADHD [75], and include differences in sleep onset and sleep latency [108]. Sleeplessness is also a frequent presenting problem for children on stimulant medications [95, 96]. It is, therefore, necessary to determine whether insomnia is a side effect of the drug, due to re-emergence of symptoms as the effects of the medication wear off, or unrelated to medication [56]. In the situation of medication wear-off, full-day cover may help to alleviate the problem.

Results from a number of studies have demonstrated that OROS MPH does not induce significant adverse effects regarding sleep [29, 100, 115, 121]. No significant differences in sleep quality were found during a 1-month study comparing OROS MPH, IR MPH and placebo [121]. Sleep quality was reported to be good or excellent for the majority of children in all three treatment groups. Sleep quality was also rated good/excellent for 71% (282/398) of children with ADHD after 1 month and 74% (134/182) after 12 months of treatment with OROS MPH [115]. Similarly, a rating of good/excellent was received for ability to fall asleep (53 and 63% at months 1 and 12, respectively). Likewise, 7 days treatment with once-daily OROS MPH and three-times daily IR MPH had similar effects on sleep quality in a double-blind, cross-over study of 64 children with ADHD. Average sleep latencies were 39, 33 and 7 min, and average true sleep durations were 7.5, 7.6 and 8 h, during administration of OROS MPH, IR MPH and placebo, respectively [100].

Growth

Growth may be impacted with stimulant therapy, and appetite reduction may be seen at the beginning of treatment [103]. Indeed, results from a retrospective review of growth data from files of all newly treated patients with ADHD in one paediatric practice, reported that during the first 6 months on stimulant medication, 86% of children had a height velocity below the age-corrected mean and there was weight loss in 76% of children [82]. Overall, the mean height deficit during the first 2 years of treatment was approximately 1 cm/year, although these effects were not cumulative and continuing [82].

A review from 2002 by Rapport et al. of quantifiable side effects associated with MPH therapy for children with ADHD has suggested that effects on height and weight are mostly transient, dose-dependent and easily rectifiable with dosage adjustments. Moreover, these side effects are considered minor from a clinical perspective considering the overall improvement in behaviour and cognitive functioning observed in most children [83]. Indeed, assessment of treatment effects with OROS MPH on growth in an open-label study found that, in general, children with ADHD gained both height and weight over time [29, 115]. Mean absolute weight increased by 2.6 kg (from 34.2 kg) during the first 12 months ($n = 407$), following a 0.1-kg decrease during the first month of treatment; mean absolute height increased steadily by 5.2 cm (from 137.1 cm) [115]. Over 21 months ($n = 178$), mean absolute weight increased by 6 kg (from 33.2 kg) and mean absolute height increased by 10.2 cm (from 135.4 cm) [29]. Clinically insignificant effects on height and weight (0.23 cm and 1.23 kg, respectively, in 21 months) have been reported in another trial, with no associated benefit from drug holidays [91]. However, the effect of stimulant therapy on growth remains a matter of some debate, particularly given the results of a recent analysis that evaluated effects of stimulant medication on growth rates in the follow-up phase of the MTA study [101]. In this analysis, the stimulant-naïve school-age children demonstrated stimulant-related decreases in growth after initiation of treatment, without evidence of growth rebound [101]. These findings are in contrast to those of a recent quantitative analysis of longitudinal studies concerning the effects of stimulant medication on the height and weight of children with ADHD, which found that, although treatment with stimulant medication leads to statistically significant delays in height and weight, it is also associated with a statistically significant attenuation of these deficits over time [27]. As with IR stimulants, the effects of long-acting stimulants on growth were found to be dose-related, and the attenuation of growth deficits was also evident for long-acting as well as IR stimulant formulations [27]. However, there is currently

no evidence to suggest whether full-day coverage might have greater effects on growth than short-term treatment. The authors of the review conclude that despite the apparent attenuation of height and weight deficits over time, and some data suggesting that ultimate adult growth parameters are unaffected by stimulant treatment, further research is required to clarify the effects of continuous treatment from childhood to adulthood [27].

Epilepsy

Although MPH is believed to lower the seizure threshold [103], clinical experience suggests that doses appropriate to clinical management of ADHD in children and adolescents with co-existing epilepsy do not increase seizure frequency, at least in those with well-controlled epilepsy [40]. More recently, a number of studies have confirmed that MPH may be safely used in patients with epilepsy and ADHD, and that there are no adverse effects on seizure severity and frequency with its use [34, 65, 107]. However, low baseline seizure rates, small numbers of patients and short observation periods limit the power of these studies to detect increases in seizure risk and further longer-term, randomized controlled studies are required [105].

Tic disorders

In a 12-month open-label study of OROS MPH in which 48 of 407 children had a prior history of tics [115], three children experienced worsening of tics, 12 no change, 10 improvement and 20 reported no tics during the study. A total of 23 of the 359 subjects with no known history of tics before the study reported new onset of tics and seven (1.7%) children discontinued treatment because of tics. The incidence of tics in children with ADHD has been calculated using five studies of OROS MPH lasting up to 2 years [76]. Data from three placebo-controlled studies reported that the incidence of tics was not significantly different between OROS MPH and placebo, while an analysis of tic episodes per patient found no correlation between OROS MPH dose and frequency of tic episodes. Although the risk of tic episodes was higher in patients with a history of tics than in those with no history of tics, data suggested that OROS MPH does not significantly induce or exacerbate tics in children with ADHD [76].

Cardiovascular risk

Sympathomimetic amines, including MPH, have the propensity to increase heart rate and blood pressure. In children, effects on heart rate and blood pressure have been shown to be mostly transient, dose-dependent and easily rectified with dosage adjustments, and are therefore,

considered minor [83]. Stimulant and non-stimulant medications used in adults with ADHD have been associated with minor, but statistically significant, changes in heart rate and blood pressure, although such changes have frequently been observed in those receiving placebo [117]. Indeed, results from a 1-month randomized controlled trial reported no significant differences in vital signs between children receiving OROS MPH, IR MPH and placebo [121]. Similarly, additional studies have reported no clinically meaningful changes in blood pressure or pulse after 1 and 2 years of treatment with OROS MPH for ADHD children with prior exposure to medication [29, 115].

Recently, there has been much discussion about the cardiovascular risks of stimulant drugs used to treat ADHD. Using the Food and Drug Administration's (FDA's) Adverse Event Reporting System, drug-related adverse events reviewed by the Drug Safety and Risk management Advisory Committee of the FDA included 25 cases (eight on MPH) of sudden death, 19 (seven on MPH) of whom were ≤ 18 years of age [73]. On autopsy, some cases had undiagnosed congenital heart disease, which renders patients vulnerable to the effects of sympathomimetic amines (such agents increase contractility and, in turn, blood pressure). After reviewing this information, the committee acknowledged the potential benefits of stimulants in the treatment of children with ADHD but emphasised "more selective and restricted use, while increasing awareness of potential hazards" [73]. However, both the Academy of Child and Adolescent Psychiatry and the American Academy of Pediatrics have concluded that sudden cardiac death in persons taking medications for ADHD is a very rare event, occurring at rates no higher than those in the general population of children and adolescents. In addition, both of these groups also noted the lack of any evidence that the routine use of ECG screening before beginning medication for ADHD treatment would prevent sudden death [78].

Psychiatric adverse events

Treatment with MPH at usual doses in children and adolescents may result in treatment-emergent psychotic or manic symptoms, such as hallucinations, delusional thinking or mania. Indeed, some psychiatric adverse events are mentioned in the labelling for various MPH products. In addition, administration of MPH may also exacerbate symptoms of behaviour disturbance and thought disorder in patients with a pre-existing psychotic disorder. This may be of particular concern given that individuals with ADHD have a high rate of comorbid psychiatric disorders, especially conduct disorder, oppositional defiant disorder, depression, anxiety, bipolar disorder, learning disabilities and other disorders, such as mental retardation, Tourette's

syndrome and borderline personality disorder [12]. Overall, such comorbidity has been shown to be associated with a high degree of impairment and a poor long-term prognosis [30, 89].

Abuse potential

There is concern that the use of stimulant medications to treat ADHD may play a role in the development of drug addiction [111]. However, when taken in clinical doses and within a clinical context there appears to be very little abuse potential [51, 103]. Rates of MPH misuse, as in its diversion towards illicit use, also appear to be low. A systematic meta-analysis of six studies on the use of stimulants in children who were followed into adolescence and young adulthood demonstrated that early stimulant treatment resulted in a protective effect against later substance use disorders, such as drug and alcohol use (odds ratio 1.9) [116]. However, a recent prospective, follow-up study, in which 112 children with ADHD were examined at baseline and again after 10 years of follow up, did not replicate these findings, instead demonstrating that stimulant treatment during childhood and adolescence neither increased nor decreased the risk for subsequent substance use disorders in young adulthood [11]. Furthermore, a recent prospective longitudinal study in which 176 white male children, aged 6–12 years, with ADHD, but without conduct disorder, were followed up in late adolescence and compared against 178 comparison subjects found that the risk of developing substance use disorder was significantly associated with age at first MPH treatment: the later the first treatment, the greater the chances of developing substance use disorder [60]. This association appeared to be accounted for by the development of antisocial personality disorder, which was not the result of age-related differences in early conduct problems [60]. The authors conclude that initiation of MPH treatment at an early age does not increase the risk of later substance abuse and may, in fact, have beneficial long-term effects [60]. Effective reduction in ADHD symptoms, such as conduct disorder, and improved academic performance and peer and family relationships may have a protective effect against the risk of later substance abuse [103]. These somewhat conflicting findings highlight the need for a better understanding of the natural history of ADHD and possible reasons for the high comorbidity observed between ADHD and substance abuse [111]. Further investigations are also required in order to examine whether low self-esteem and insecurity amongst individuals with ADHD, which may develop due to failures at school and in personal relationships [103], might be prevented or ameliorated by early treatment with an extended period of symptom management over the day.

Suicide

Several studies have shown a possible association between ADHD and suicide [43, 46]. Indeed, results from a review of the literature from 1966 to 2003 reported that a diagnosis of ADHD is associated with an increased risk of suicide in young males by worsening comorbid conditions, particularly conduct disorder and depression [43]. However, to date, there is no known association between administration of MPH and the risk of suicide.

Rebound effects

One of the major challenges of MPH treatment is ‘wearing-off’ or rebound effects [31]. This phenomenon may be reduced by the unique pattern of MPH delivery by OROS MPH, which minimises the ‘peaks and troughs’ in plasma concentrations associated with more frequent dosing and provides 12-h coverage [99]. Indeed, this has been specifically reported in a 44-year-old female patient who experienced severe rebound phenomena with pronounced concentration disturbances, unrest and dysphoric mood when treated three-times daily IR MPH which stopped when she was switched to once-daily OROS MPH [88].

General concerns of stimulant use

Some of the potential risks associated with MPH treatment (e.g. growth effects) may incite legitimate emotional reactions in parents, and decisions about medication may, therefore, be made without a clear analysis of the associated benefit:risk ratio. Concerns over the long-term effects of treatment may be exacerbated by the fact that MPH and amphetamine are stimulants, which are controlled substances [99]. Thus, in the minds of some patients and parents, links are made between the medication and drug abuse with its associated problems and consequences. Such beliefs may encourage parents to supervise treatment, leading to older children and adolescents reacting against increased parental control. Moreover, parental scepticism about the value and appropriateness of stimulant therapy may affect the child’s attitude and overall compliance. The public, therefore, needs to be reassured that the efficacy and tolerability of MPH is generally proven; LA preparations may help overcome some concerns, since such formulations can enable symptoms to be conveniently controlled over the full day using a single dose.

Balancing the risk:benefit ratio

While the importance of treating ADHD is established [25, 79, 86, 103] and stimulants are usually the first-line treatment [79], a number of factors need to be taken into

consideration when selecting a treatment and formulation for an individual, including concordance, compliance and difficulties with multiple doses and the preference of patients and caretakers [25]. Studies on the OROS MPH preparation, for example, have demonstrated symptomatic remission, improvement in academic achievement, improved social skills and a reduction in parental stress [42, 77, 94, 99, 115].

Although the individuals with ADHD and their families are of primary concern, the benefits of treatment may also extend to the utilisation and cost of health care resources; in the US these are significantly greater for children and adolescents with ADHD than for people without ADHD, making treatment cost-effective relative to no drug treatment [15, 25, 35, 57, 61]. However, estimates are likely to under-estimate the true costs of caring for children with this condition because much ADHD-related care occurs within school and mental health settings. OROS MPH has been reported to be associated with an incremental cost-effectiveness ratio (ICER) of 9200 GBP per quality adjusted life-year (QALYs) gained, i.e. more QALYs and a net cost saving, compared with IR MPH, Equasym XL, atomoxetine and behavioural therapy. A study conducted in The Netherlands regarding the cost-effectiveness of treatment with OROS MPH for youths with ADHD for whom treatment with IR MPH is suboptimal concluded that OROS MPH was a cost effective treatment; the 10-year total costs between treatments were comparable (OROS MPH, 16,015 €; IR MPH 15,739 €), and the ICER for OROS MPH was 2004 € per QALY [26]. Additionally, a cost consequence analysis of the management of ADHD in the UK revealed that starting ADHD treatment with behavioural therapy alone resulted in the highest annual cost (3,453 €), while starting ADHD treatment with IR MPH alone (2,138 €) and OROS MPH alone (2,187 €) generated similar costs [110].

Conclusions

For children and adolescents with ADHD, there is a need for treatment approaches that take into account the 24-h impact of the disorder and include all-day coverage with effective medication. Time after school, when life may be less structured, is just as important as school time for a patient with ADHD in terms of developing social and interpersonal skills. A number of long-acting MPH formulations are currently available, which have been shown to provide symptom control throughout the active day. Moreover, such formulations avoid the embarrassment of having to take medication in public and the associated stigma attached to having a psychiatric condition requiring medication.

It is envisaged that treatments that provide effective symptom control will also have the potential to improve patients' social functioning and overall quality of life. However, whilst much current research in ADHD has focused on the objective management of symptoms, the effect of stimulant medication on the everyday functioning and well-being of children with ADHD (e.g. ability to undertake homework, participate in after-school activities, develop social and personal skills and engage with friends and family) remains relatively unexplored. As such, further research, especially long-term studies, are required to examine the impact of stimulant medications on these important outcomes measures.

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